NONPARAMETRIC TESTS OF INDEPENDENCE FOR CENSORED DATA WITH APPLICATION TO HEART TRANSPLANT STUDIES

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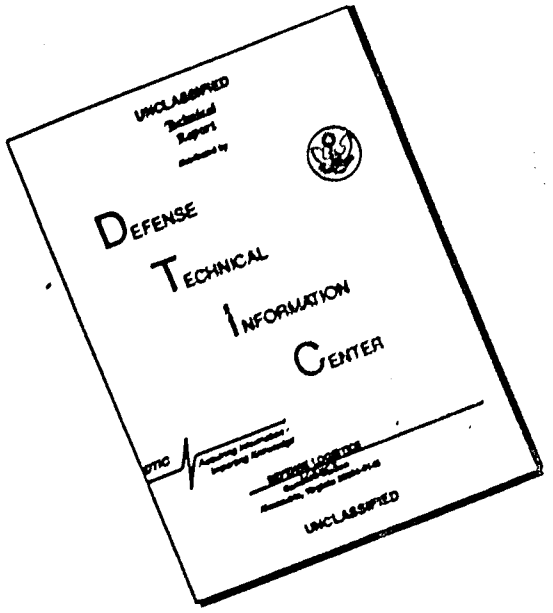

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A patient officially selected as a heart transplant candidate, in the Stanford Heart Transplant Program, will receive a transplant if he survives until a donor is found. He will not receive a new heart if he dies before a donor is found, or if he is "deselected" (for showing noteworthy improvement). For a candidate who does not receive a transplant, the available data include his survival time (in days from the date of acceptance into the program) and

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if deselected, his date of deselection. For a candidate who does receive a transplant, the available data include the waiting time for a donor and the survival time from the date of operation. Waiting time and survival time variables may be censored at the closing date of the study. Turnbull and Brown [14] and Turnbull, Brown and Hu [15] considered the question: Does cardiac transplantation at Stanford prolong life? [They found there was not sufficient evidence to support a "Yes" answer; in fact their analyses showed that the post-transplant survival times of transplant patients were consistent with pre-transplant experience of all heart candidates.] Here we investigate which variables are correlated with post-transplant survival length. Variables considered are sex, age, waiting time for donor, and date of transplant. These investigations lead to new nonparametric tests of independence for censored data.

NONPARAMETRIC TESTS OF INDEPENDENCE FOR CENSORED DATA WITH APPLICATIONS TO HEART TRANSPLANT STUDIES

by

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4 This research will also appear as a Stanford University Technical Report under the Public Health Service grant referenced in 2.

Nonparametric Tests of Independence for Censored Data with Applications to Heart Transplant Studies

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Abstract. A patient officially selected as a heart transplant candidate, in the Stanford Heart Transplant Program, will receive a transplant if he survives until a donor is found. He will not receive a new heart if he dies before a donor is found, or if he is "deselected" (for showing noteworthy improvement). For a candidate who does not receive a transplant, the available data include his survival time (if any) from the date of acceptance into the program) and, if deselected, his date of deselection. For a candidate who does receive a transplant, the available data include the waiting time for a donor and the survival time from the date of operation. Waiting time and survival time variables may be censored at the closing date of the study. Turnbull and Brown [14] and Turnbull, Brown, and Hu [15] considered the question: Does cardiac transplantation at Stanford

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prolong life? [They found there was not sufficient evidence to support a "Yes" answer; in fact their analyses showed that the post-transplant survival times of transplant patients were consistent with pre-transplant experience of all heart candidates.] Here we investigate which variables are correlated with post-transplant survival length. Variables considered are sex, age, waiting time for donor, and date of transplant. These investigations lead to new nonparametric tests of independence for censored data.

1. Introduction. Heart transplantation has held an extraordinary fascination for both layman and medical scientist ever since the first operation by Barnard in 1967. After the first flurry of operations, two programs in the United States continued to accumulate experience in transplantation, one at Baylor University and one at Stanford University. The survival experience of transplant patients at Baylor was summarized by Messmer, et al [13]. They concluded that survival time of their transplant patients was extended but the additional life time was not worth the attending cost, including trauma; the program was discontinued. The Stanford experience was summarized by Clark, et al [2]. They also concluded that transplantation extended life and the program at Stanford continues, with one to three new transplants a month.

Gail [7] examined the Messmer, et al [13] and Clark, et al [2] papers and found that both papers employed a method of analysis that is highly biased. Briefly, the analyses compared survival times for

heart transplant patients with the survival times of transplant candidates who died before a donor heart was found.

Turnbull and Brown [14] re-analyzed the Stanford data, taking Gail's criticism into account, and, recently, Turnbull, Brown and Hu [15] have analyzed the Stanford data again, summarizing the data as of March 1, 1973. They concluded that the survival times of heart transplant patients are quite consistent with pre-transplant experience of all pre-transplant heart candidates selected, but that no definite conclusion can be reached on the question of life-extending effects of transplantation, because there is too little long-time pre-transplant data available. However, there is good evidence that transplantation does not shorten expected survival time to any great extent, and the quality of life for some survivors is remarkably enhanced.

The analyses of Turnbull, et al ([14], [15]) did not consider which variables were correlated with the length of post-transplant survival. Here we address this question of correlation considering, in particular, the variables sex, age at transplant date, date of transplant, and waiting time for a donor. The investigation of a possible correlation between date of transplant and post-transplant survival is of special interest because it can be viewed as an examination of a trend in the expected survival time of transplant patients (with an increasing trend possibly reflecting improvement in surgical techniques, in the methods of selecting transplant candidates, and in

monitoring and caring for the post-transplant patients).

Our approach is via Kendall's [12] rank correlation statistic. This statistic, however, has to be modified to accommodate right censoring of the dependent variable, typically found in clinical survival studies. Two conditionally distribution-free tests are presented; one (Section 3) is analogous to Gehan's [8] adaptation of the Wilcoxon two sample statistic to censored data and the other (Section 4) is analogous to Efron's [6] adaptation of the Wilcoxon two sample statistic to censored data. The conditionally distribution-free tests of Sections 3 and 4 are based on an independence assumption concerning the basic variables (whose independence is being tested) and the censoring variable. This assumption [Assumption (A)--see Section 3] will not be satisfied in certain situations of interest. Hence, in Section 5, we relax this assumption and provide a "pseudo" conditional test. This test, however, does not possess the distribution-free property. Section 6 summarizes the applications of these techniques to questions of interest in the Stanford Heart Transplant Program. Robustness comments are made in Section 7.

2. Data description. The starting date for a patient will be the date on which he is declared a transplant candidate in a team conference, initiating the search for a donor. The data for the 82 candidates admitted to the program, as of March 1, 1973, are given in Table 1. For patients who died before a donor was found for them and for those still awaiting a heart, we give their birth date, date of

declared acceptance into the program, sex, and the number of days of survival (to death or to the closing date for analysis, March 1, 1973). We also indicate whether the patient is alive or dead at the closing date. For patients receiving a new heart we give the birth date, date of acceptance, sex, days to transplant, days from transplant to death or closing date, and state (dead or alive) at closing date.

Table 1: Acceptance dates, birth dates, sex, survival times, and times to transplant for Stanford Program patients. (Closing date: March 1, 1973)

Nontransplant Patients (30)

Birth Date			Sex	Acceptance Date			T_1[1]	alive = a dead = d
Mo.	Day	Yr.		Mo.	Day	Yr.		
5	20	28	M	9	13	67	5	d
1	10	37	M	11	15	67	49	d
3	2	16	M	1	2	68	5	d
7	28	47	M	5	10	68	17	d
11	8	13	M	6	13	68	2	d
3	27	23	M	8	1	68	39	d
6	11	21	F	8	9	68	84	d
7	9	15	M	9	17	68	7	d
12	4	14	M	9	27	68	0	d
6	29	48	M	10	28	68	35	d
10	4	09	M	11	18	68	36[2]	d
10	18	38	M	5	1	69	1400[2]	a
2	6	19	F	7	14	69	34	d
10	4	14	M	8	23	69	15	d
8	4	26	M	1	21	70	11	d
3	13	34	M	8	21	70	2	d
6	1	27	F	10	22	70	1	d
5	2	28	M	11	30	70	39	d
1	23	15	M	2	5	71	8	d
1	24	30	M	4	25	71	101	d
9	16	23	M	7	2	71	2	d
6	8	30	M	9	13	71	148[3]	d
8	19	42	M	11	1	71	427[3]	a

Birth Date Mo.	Day	Yr.	Sex	Acceptance Date Mo.	Day	Yr.	T_1[1]	alive = a dead = d
5	12	19	M	12	4	71	1[4]	d
8	1	32	M	12	9	71	68[4]	d
1	2	19	M	3	20	72	31	d
7	25	20	M	9	29	72	1	d
8	27	31	M	10	6	72	20	d
2	20	24	F	11	3	72	118	a
2	18	19	M	11	30	72	91	a

Transplant Patients (52)

Birth Date Mo.	Day	Yr.	Sex	Acceptance Date Mo.	Day	Yr.	T_2[1]	T_3[1]	alive = a dead = d
9	19	13	M	1	6	68	0	15	d
12	23	27	M	3	28	68	35	3	d
8	29	17	M	7	12	68	50	624	d
2	9	26	M	8	11	68	11	46	d
8	22	20	F	8	15	68	25	127	d
2	22	14	F	9	19	68	16	61	d
9	16	14	M	9	20	68	36	1350	d
5	16	19	M	10	26	68	27	312	d
12	27	11	M	11	1	68	19	24	d
10	19	13	M	1	29	69	17	10	d
9	29	25	M	2	1	69	7	1024	d
6	5	26	M	3	18	69	11	39	d
12	2	10	M	4	11	69	2	730	d
7	7	17	M	4	25	69	82	136	d
2	6	36	M	4	28	69	24	1379	a
5	30	15	M	6	7	69	70	1	d
9	20	24	F	8	19	69	15	836	d
4	2	05	M	8	29	69	16	60	d
1	1	21	M	11	27	69	50	1140	a
5	24	29	M	12	12	69	22	1153	a
5	1	21	M	4	4	70	45	54	d
10	24	08	M	4	25	70	18	47	d
11	14	28	M	5	5	70	4	0	d
11	12	19	M	5	20	70	1	43	d
11	30	21	M	5	25	70	40	971	a
4	30	25	M	8	19	70	57	868	a
10	30	34	M	1	5	71	0	44	d

Birth Date Mo.	Day	Yr.	Sex	Acceptance Date Mo.	Day	Yr.	T_2	T_3	alive = a dead = d
6	1	22	F	1	10	71	1	780	a
12	28	23	M	2	2	71	20	51	d
6	21	34	M	2	15	71	35	710	a
3	28	25	M	2	15	71	82	663	a
6	29	22	M	3	24	71	31	253	d
2	27	24	M	7	2	71	40	147	d
2	24	19	M	8	9	71	9	51	d
12	5	32	M	9	3	71	66	479	a
9	17	23	M	9	23	71	20	322	d
5	12	30	M	9	29	71	77	442	a
10	29	22	M	11	18	71	2	65	d
4	15	39	M	12	12	71	26	419	a
4	9	23	M	2	1	72	32	362	a
11	19	20	M	3	6	72	13	64	d
9	3	52	M	3	23	72	56	228	d
1	10	27	M	4	7	72	2	65	d
6	5	24	M	6	1	72	9	264	a
6	17	19	M	6	17	72	4	25	d
2	22	25	M	7	21	72	30	193	a
11	22	45	M	8	14	72	3	196	a
5	13	16	M	9	11	72	26	63	d
7	20	43	M	9	18	72	4	12	d
9	3	20	M	10	4	72	45	103	a
6	27	26	M	12	6	72	25	60	a
2	21	20	M	1	12	73	5	43	a

[1] T_1 = days to death or closing date.
T_2 = days to transplant.
T_3 = days from transplant to death or closing date.

[2] Deselected 8/21/69.

[3] Deselected 2/02/72 (also, for this patient only, survival experience is known only up to 1/1/73 so that the T_3 = 427 entry is measured from 11/1/71 to 1/1/73 rather than 3/1/73).

[4] Deselected 2/04/72.

Source: E. Dong ([5], 1973)

3. Simple scores modification of Kendall's rank correlation statistic. For data consisting of n pairs $(X_1,Y_1),\ldots,(X_n,Y_n)$ the hypothesis of independence of X and Y can be tested using Kendall's [12] rank correlation statistic

$$S = \sum_{i=1}^{n} \sum_{j=1}^{n} a_{ij} b_{ij} , \tag{1}$$

where $a_{ij} = 1$ if $X_i > X_j$, 0 if $X_i = X_j$, -1 if $X_i < X_j$, $b_{ij} = 1$ if $Y_i > Y_j$, 0 if $Y_i = Y_j$, -1 if $Y_i < Y_j$. If, however, either X or Y (or both) is censored, we may be unable to compute certain of the a's or b's. In our heart transplant studies we encountered situations where one of the variables (say Y) was right-censored; for convenience and simplicity we develop our tests for this case. Modifications in situations where X and Y are both right-and left-censored are notationally more complex but can be developed in a similar manner.

When the Y variable is right-censored, our observed paired data may be characterized by the vector $W = \{(X_1,Z_1,\delta_1),\ldots,(X_n,Z_n,\delta_n)\}$ where, for $i = 1,\ldots,n$,

$$Z_i = \text{minimum } \{Y_i,B_i\} , \tag{2}$$

and

$$\delta_i = \begin{cases} 1 & \text{if } Z_i = Y_i \text{ (that is, } Y_i \text{ is uncensored)} \\ 0 & \text{if } Z_i = B_i \text{ (that is, } Y_i \text{ is censored at a known value, } B_i). \end{cases} \tag{3}$$

For example, in our study of a possible correlation between sex and length of post-transplant survival, $X_i = 1$ if patient i is male and 0 if female, and Y_i is the number of days patient i survived after transplant. If patient i dies before the closing date, Y_i is uncensored and $Z_i = Y_i$. If, however, patient i is still alive on the closing date, then Y_i is (for our present purposes) censored and we instead observe $Z_i = B_i$, the number of days from the date of transplant to the closing date. [In the notation of Table 1, $\delta_i = 1$ corresponds to the letter "d," $\delta_i = 0$ corresponds to "a."]

For the case where Y is right-censored, we adjust the definition of the b's as follows:

$$(4) \qquad b_{ij} = \begin{cases} 1 & \text{if } Y_i \overset{d}{>} Y_j, \\ 0 & \text{if } Y_i = Y_j \text{ or if "uncertain"}, \\ -1 & \text{if } Y_i \overset{d}{<} Y_j. \end{cases}$$

In (4), $Y_i \overset{d}{>} Y_j$ (read "Y_i is definitely greater than Y_j") means that, on the basis of $Z_i, Z_j, \delta_i, \delta_j$, we can infer that $Y_i > Y_j$. The notation $Y_i \overset{d}{<} Y_j$ is defined similarly, and $b_{ij} = 0$ if we can infer that $Y_i = Y_j$ or if, because of censoring, we cannot be sure of the Y_i, Y_j ordering. We have that (i) $Y_i \overset{d}{>} Y_j$ if (a) $\delta_j = 1$ and $Z_i > Z_j$, or (b) $\delta_i = 0$, $\delta_j = 1$, and $Z_i = Z_j$. We have (ii) $Y_i \overset{d}{<} Y_j$ if (c) $\delta_i = 1$ and $Z_i < Z_j$, or (d) $\delta_i = 1$, $\delta_j = 0$, and $Z_i = Z_j$. For (i), $b_{ij} = 1$; for (ii), $b_{ij} = -1$. If both (i) and (ii) are not true, then $b_{ij} = 0$.

The significance of the statistic S, for testing independence, can be obtained by seeing where the observed value of S ($S(w)$ say) falls in the permutation distribution obtained by computing $n!$ values of S, one value for each of the $n!$ possible permutations of the $\{(Z_1,\delta_1).....(Z_n,\delta_n)\}$ observations (keeping the X's fixed). Consider then the group G of $n!$ transformations with typical member

$$g_{i_1 \ldots i_n}(W) = \{(X_1,Z_{i_1},\delta_{i_1}).....(X_n,Z_{i_n},\delta_{i_n})\} ,$$

where $(i_1.....i_n)$ is a permutation of $(1,...,n)$. As a reference point for determining the significance of $S(w)$, we consider the use of the conditional measures

$$P_c(W = g_{i_1,....,i_n}(W)) = (n!)^{-1} , \tag{5}$$

for each permutation $(i_1,...,i_n)$ of $(1....,n)$.

The use of (5) can be justified if the independence of X and Y implies the independence of X and (Z,δ), so that when the hypothesis of X,Y independence is true, for each $g \in G$, $g(W)$ would have the same distribution as W. In developing the conditional distribution-free tests of Sections 3 and 4, we thus take as a basic assumption

(A) When X and Y are independent, X and (Z,δ) are independent.

Whether or not assumption (A) is satisfied in practice depends on the joint distribution of (X,Y,B). [An assumption that implies (A), but

is unnecessarily restrictive is (A'): When X and Y are independent, X, Y, and B are mutually independent.] A rough (but not uniformly valid) rule is that Assumption (A) is a reasonable assumption to make when the independence of X and Y implies the independence of X and B. For example, with $X_i = 1$ if patient i is male and 0 if female, and Y_i = number of post-transplant survival days for patient i, Assumption (A) is reasonable. However, if we define X_i to be the date of transplant (and keep Y as above), then since B_i = number of days from X_i to closing date, it is clear that X and B have a correlation of -1 whether X and Y are independent or not. (We can write $B_i = T - X_i$ where T is a fixed constant.) In this case, even if X and Y are independent, X and (Z,δ) are dependent and (5) is not justified.

When Assumption (A) is satisfied, our α-level test is defined as follows. Let $S^{(1)}(w) \leq \cdots \leq S^{(n!)}(w)$ denote the n! ordered values of $S(g(w))$ for $g \in G$. Let $\varphi(w)$ denote the probability of rejecting the hypothesis of independence when $W = w$. We set

$$\varphi(w) = \begin{cases} 1 & \text{if } S(w) > S^{(m)}(w), \\ r(w) & \text{if } S(w) = S^{(m)}(w), \\ 0 & \text{if } S(w) < S^{(m)}(w), \end{cases} \tag{6}$$

where $m = n! - [n!\alpha]$, $[x]$ is the greatest integer less than or equal to x and $r(w)$ is selected to give the test size α.

Under Assumption (A), the test defined by (6) is a one-sided conditionally distribution-free test of independence versus the alternative of positive association between X and Y. One-sided tests versus negative association and two-sided tests are similarly defined.

For large n, the following approximation to the conditional distribution of S can be used. Under suitable regularity (a sufficient condition is that $\Sigma a_{ij}a_{ij'}$ and $\Sigma b_{ij}b_{ij'}$ each be of the order of n^3) the statistic S is conditionally asymptotically normal with conditional mean

$$E(S) = 0 \tag{7}$$

and conditional variance

$$\begin{aligned} \mathrm{Var}(S) = {} & 4[n(n-1)(n-2)]^{-1}(\Sigma a_{ij}a_{ij'} - \Sigma a_{ij}^2)(\Sigma b_{ij}b_{ij'} - \Sigma b_{ij}^2) \\ & + 2[n(n-1)]^{-1}(\Sigma a_{ij}^2)(\Sigma b_{ij}^2) . \end{aligned} \tag{8}$$

In the above summations, each subscript is summed from 1 to n. The conditional mean, variance, and asymptotic normality follow directly from Daniels [4].

In the special case when the distribution of (X,Y) is continuous and there is no censoring, exact critical values of $S/2$, for $n = 4(1)40$, can be obtained from Table I of Kaarsemaker and van Wijngaarden [10], which also appears as Table A.21 of Hollander and Wolfe [9].

If we set $X_i = 1$ if ith patient is male and 0 if female, then Assumption (A) is reasonable. This dichotomy puts the problem in

the framework of the two sample location problem for censored data, for we are then comparing the Y variable in the male and female populations. In such a case, the conditionally distribution-free test given by (6) reduces to Gehan's [8] procedure. Of course, Assumption (A) is reasonable for other types of X variables (e.g. physical status at date of transplant, or degree of tissue match with donor).

4. Kaplan-Meier scores modification of Kendall's rank correlation statistic. The b's defined by (4) ignore certain available information. For example, suppose, for the moment, we identify Z with the post-transplant survival variable T_3 of Table 1. Consider patients 15 and 52, with Z values 1379 and 43 respectively. The approach of Section 3 scores $b_{15,52} = 0$ since $\delta_{15} = \delta_{52} = 0$. That is, since both patients were alive at the closing date, we are uncertain as to which one will accumulate more post-transplant life. However, since patient 15 has been best, to date, in terms of post-transplant survival in the Stanford Program, one feels it is likely that Y_{15} will exceed Y_{52}. To quantify this, we follow Efron [6] and utilize the Kaplan-Meier ([11], [6], [3]) estimator of the true survival function.

Let $Z_{(1)} \leq \cdots \leq Z_{(n)}$ denote the ordered values of the Z's. Then the nonparametric maximum likelihood estimator of the survivorship function $H(t) = P(Y > t)$ for $t > 0$ is given by:

$$\hat{H}(t) = \prod_{r} \{(n-r)/(n-r+1)\} \quad , \tag{9}$$

where r runs through those positive integers for which $Z_{(r)} \leq t$ and $Z_{(r)}$ is an uncensored observation. Our Kaplan-Meier adjusted b scores are given in Table 2.

Table 2. Values of b_{ij} based on the Kaplan-Meier estimator.

(δ_i, δ_j)	$Z_i > Z_j$	$Z_i = Z_j$	$Z_i < Z_j$
(1,1)	1	0	-1
(0,1)	1	1	$2\{\hat{H}(Z_j)/\hat{H}(Z_i)\}-1$
(1,0)	$1-2\{\hat{H}(Z_i)/\hat{H}(Z_j)\}$	-1	-1
(0,0)	$1-\{\hat{H}(Z_i)/\hat{H}(Z_j)\}$	$1-\{\hat{H}(Z_i)/\hat{H}(Z_j)\}$	$\{\hat{H}(Z_j)/\hat{H}(Z_i)\}-1$

Note that, except for the case $Z_i = Z_j$, the b_{ij} scores are given by

$$b_{ij} = 2P\{Y_i > Y_j | Z_i, Z_j, \delta_i, \delta_j, \hat{H}\}-1 \quad ,$$

where the conditional probability is interpreted as if Y_i and Y_j were actually drawn from $\hat{H}$.

The Kaplan-Meier scores conditional test is based on S_n and is defined by (6), where now the b's are obtained from Table 2 and the a's are as defined in Section 3. Under Assumption (A), the test

is conditionally distribution-free. With the b scores given by Table 2, the conditional mean and variance for the normal approximation are given by (7) and (8), respectively.

5. A pseudo-conditional test. In Section 3 we pointed out that Assumption (A) was not satisfied when X = date of transplant and Y = length of post-transplant survival. The hypothesis of independence of X and Y is of interest because a positive association would suggest a beneficial trend in post-transplant survival since initiation of the Stanford Program. Since the procedures of Sections 3 and 4 are not applicable in this situation, we were led to the following "pseudo-conditional" test.

When $\delta_i = 0$, we know that $Y_i > B_i$, and we also know B_i. We can then "fill in" the unknown Y_i value by taking a random value from the distribution function defined by

$$\hat{P}(Y_i > t | Y_i > B_i) = \hat{H}(t)/\hat{H}(B_i) \quad , \tag{10}$$

where $\hat{H}(t)$ is the Kaplan-Meier estimator defined by (9). However, the random distribution functions defined by (9) and (10) are not continuous and there is also ambiguity in the Kaplan-Meier estimator when $Z_{(n)}$, the largest Z value, corresponds to a censored value. In that case, Kaplan and Meier suggested that for $t > Z_{(n)}$, $\hat{H}$ should be regarded as being between $\hat{H}(Z_{(n)})$ and 0, but not further specified.

In order to sample from $\hat{H}$, and to avoid obtaining tied values, we

completed and adjusted $\hat{H}$ to H^* (say) as follows. We formed a polygonal curve, connecting the points $(Z_{(r)},\hat{H}(Z_{(r)}))$, where r runs through the subscripts corresponding to uncensored values. We then defined $H^*(t)$ to be the polygonal curve up to $Z_{(n)}$, and beyond $Z_{(n)}$

$$H^*(t) = \exp\{[\ell n\ \hat{H}(Z_{(n)})]t/Z_{(n)}\}\ ,\quad t > Z_{(n)}\ . \tag{11}$$

This corresponds to fitting an exponential to the tail as follows. For $t > Z_{(n)}$, H^* is given by the probability $H^*(t) = \exp\{-t/\theta\}$, where θ is chosen so that for $t = Z_{(n)}$, $\exp\{-t/\theta\} = \hat{H}(Z_{(n)})$, the Kaplan-Meier estimate for $t = Z_{(n)}$. We used this adjustment for all cases, that is, when $Z_{(n)}$ corresponded to a censored value and when $Z_{(n)}$ corresponded to an uncensored value. Let Y_i^* denote a random value sampled from the distribution defined by

$$P(Y_i^* > t) = H^*(t)/H^*(B_i)\ , \tag{12}$$

where i runs through those subscripts for which $\delta_i = 0$.

Our pseudo-conditional test consists of applying the usual permutation test based on S to the uncensored "sample" $[(X_i,Y_i), i$ such that $\delta_i = 1, (X_i,Y_i^*), i$ such that $\delta_i = 0]$. If choosing the Y^*'s by a random mechanism is too distasteful to the user, an alternative suggestion is to take Y_i' to be the median of the distribution defined by (12).

6. Applications. In this section we give the results of the following correlation analyses: (i) sex versus post-transplant survival time, (ii) age at transplant versus post-transplant survival time, (iii) date of transplant versus post-transplant survival time, (iv) waiting time for a donor versus post-transplant survival time, (v) date of acceptance versus waiting time for a donor, (vi) date of acceptance versus sex, (vii) date of acceptance versus age at acceptance date.

The tests advocated in Sections 3, 4, and 5 are referred to as simple adjusted (SA), Kaplan-Meier adjusted (KMA), and pseudo-conditional (PC), respectively. Assumption (A) of Section 3 is not reasonable for projects (iii) and (v) and thus the SA and KMA procedures are suspect in those cases; nevertheless, for completeness, we report the SA and KMA results. In projects (vi) and (vii) there is no censoring and SA, KMA, and PC all reduce to the same procedure, namely the usual test of independence based on Kendall's S.

Our sample sizes are $n = 52$ (projects (i)-(iv)) and $n = 82$ (projects (v)-(vii)). Thus n is too large to perform $n!$ permutations. Our results are stated in terms of the normal approximation

and an approximation to the permutation test based on a random sample of 1000 permutations. In addition to giving the one-sided significance probability (P value) associated with S, we include the value of

$$(13) \qquad r = S/\{\sum_{i,j} a_{ij}^2 \sum_{i,j} b_{ij}^2\}^{1/2},$$

the latter being interpretable as a measure of correlation. The results are summarized in Table 3.

Table 3. Significance probabilities for correlation analyses.

Project	Procedure	S	Normal deviate	P (Normal approx.)	P (1000 permutations)	r
i	SA	-72	-.665	.253	.291	-.080
i	KMA	-62.1	-.553	.290	.322	-.067
i	PC	-52	-.446	.328	.349	-.052
ii	SA	-484	-2.056	.020	.022	-.205
ii	KMA	-521.6	-2.138	.016	.019	-.214
ii	PC	-588	-2.320	.010	.008	-.232
iii	SA	428	1.818	.035	.033	.181
iii	KMA	404.1	1.656	.049	.048	.166
iii	PC	524	2.068	.019	.017	.198
iv	SA	642	2.729	.0032	.003	.273
iv	KMA	657.7	2.697	.0035	<.001	.272
iv	PC	684	2.701	.0035	.001	.260
v	SA	-226	-.567	.285	.277	-.040
v	KMA	-208.9	-.457	.324	.315	-.036
v	PC	-404	-.809	.209	.187	-.061
vi	SA	276	1.078	.140	.164	.098
vii	SA	-338	-.677	.249	.236	-.051

(i) Sex versus post-transplant survival: Here $X = 1$ if the patient is male, 0 if female, and Z is the minimum of the time from transplant to death and the time from transplant to closing date.

Eighteen observations, corresponding to those patients who received transplants before the closing date and were alive at the closing date, are censored. The data are sparse for detecting sex differences since only four of the fifty-two transplant patients are women. The data do not indicate a significant correlation between sex and post-transplant survival. The Kaplan-Meier estimator $\hat{H}(t)$ of $P\{Y > t\}$, where Y = post-transplant survival time, is given in Table 4. In addition to $\hat{H}(t)$, Table 4 contains an estimator of the standard deviation of $\hat{H}(t)$. The estimator, given by Kaplan and Meier [11], is

$$\widehat{SD}(\hat{H}(t)) = \hat{H}(t)\{\Sigma_r[(n-r)(n-r+1)]^{-1}\}^{1/2}, \tag{1-}$$

where $Z_{(1)} \leq \cdots \leq Z_{(n)}$ are the ordered Z's, and r runs through those positive integers for which $Z_{(r)} \leq t$ and $Z_{(r)}$ is an uncensored observation.

The Kaplan-Meier estimator is based on the assumption that the Y's (of which only 34 are observable here) are independent and identically distributed. There is some evidence (see project (iii)) that in fact there is a trend in the Y's and so this assumption is probably not valid. Nevertheless, we need $\hat{H}(t)$ in order to apply the KMA and PC procedures. Furthermore, Table 4 is informative in its own right.

Table 4. Kaplan-Meier estimator of the post-transplant survival distribution.

t (days)	$\hat{H}(t)$	$\hat{SD}(\hat{H}(t))$
0	.981	.019
1	.962	.027
3	.942	.032
10	.923	.037
12	.904	.041
15	.885	.044
24	.865	.047
25	.846	.050
39	.827	.052
43	.808	.055
44	.788	.057
46	.768	.059
47	.749	.060
51	.709	.063
54	.689	.065
60	.670	.066
61	.650	.067
63	.629	.068
64	.609	.068
65	.568	.070
127	.547	.070
136	.526	.071
147	.505	.071
228	.482	.071
253	.459	.071
312	.435	.071
322	.410	.071
624	.379	.073
730	.341	.075
836	.299	.077
1024	.239	.081
1350	.119	.094

(ii) Age at transplant versus post-transplant survival: Here X = age at transplant, Z is as in project (i). Procedures SA, KMA, and PC all indicate a small but significant negative correlation

between age at transplant and post-transplant survival (see Table 3).

(iii) Date of transplant versus post-transplant survival: Here X = date of transplant, Z is as in project (i). Assumption (A) is not valid, but we applied procedures SA and KMA to compare them with the PC test. The analyses (see Table 3) suggest a modest but significant positive correlation between post-transplant survival time and date of transplant, with more recent candidates in the program generally faring better than earlier candidates. One would like to attribute this trend to improved surgical technique, and post-surgical care, but it may be due to other factors as well, such as selection of hardier patients or more appropriate candidates in recent years of the program. Projects (v)-(vii) investigate whether there has been a change over time in waiting time for a donor, sex of the candidates, and age of the candidates.

(iv) Waiting time for a donor versus post-transplant survival time: Here X = time from acceptance to transplant, Z is as in project (i). Procedures SA, KMA, and PC all indicate a significant positive correlation between waiting time and post-transplant survival (see Table 3). One possible explanation: Those patients that have to wait a long time for a donor (and survive to receive a heart) are selected for hardiness by this process, and might be expected to survive longer.

(v) Date of acceptance versus waiting time for a donor: Here X = acceptance date and Z is the minimum of the times to death,

transplant, deselection, and closing date. The uncensored values here are those Z's corresponding to patients who received transplants. Thirty of the eighty-two observations are censored. There is no evidence (see Table 3) of a trend in waiting time for a donor. The Kaplan-Meier estimator of $P\{Y > t\}$, where Y = waiting time for a donor, is given in Table 5.

Table 5. Kaplan-Meier estimator of waiting time for a donor distribution.

t (days)	$\hat{H}(t)$	$\hat{SD}(\hat{H}(t))$
0	.976	.017
1	.951	.024
2	.912	.032
3	.899	.034
4	.859	.040
5	.845	.041
7	.831	.043
9	.803	.046
11	.774	.048
13	.759	.050
15	.745	.051
16	.715	.053
17	.700	.054
18	.685	.055
19	.670	.056
20	.639	.057
22	.624	.058
24	.608	.059
25	.577	.060
26	.546	.060
27	.530	.061
30	.515	.061
31	.499	.061
32	.483	.061
35	.450	.061
36	.432	.061
40	.393	.062

t (days)	$\hat{H}(t)$	$\hat{SD}(\hat{H}(t))$
45	.354	.061
50	.312	.061
56	.291	.060
57	.270	.059
66	.248	.059
70	.225	.057
77	.203	.056
82	.158	.052

(vi) Date of acceptance versus sex: Here neither variable is censored. The independence test yields a non-significant trend ($P = .14$) with the indication of a slight tendency toward choosing male candidates as the program progresses.

(vii) Date of acceptance versus age at acceptance date: Neither variable is censored, and, on the basis of the S test, one is led to accept the hypothesis of no association. See Table 3.

7. Robustness comments. The SA and KMA procedures are exact when Assumption (A) is satisfied. The PC procedure is not exact but a hint of its robustness can be obtained by comparing it with SA and KMA for situations where Assumption (A) is valid. Projects (i) and (ii) furnish such comparisons, and there is reasonable agreement (see Table 3). For project (iv), where the deviation from Assumption (A) is mild, SA, KMA, and PC are also in good agreement.

In project (iii), the deviation from Assumption (A) is strong; a -1 correlation between X and B exists (whether or not X and Y are independent). Here the significance probabilities achieved by

SA and KMA may overemphasize the significance of a positive correlation between X and Y. The fact that the P value for PC is even smaller than those for SA and KMA may be in part due to the exponential tail adjustment (see (11), Section 5) of the Kaplan-Meier estimator. The exponential tail tends to be optimistic about post-transplant survival prediction--especially for those censored values corresponding to transplants that occurred shortly before the closing date.

In view of the importance of project (iii), the following, more conservative, approach to post-transplant survival prediction was also used. After connecting the consecutive points $(Z_{(r)}, \hat{H}(Z_{(r)}))$ as in Section 5, the line connecting the points corresponding to the two largest uncensored values was extended downward until it intersected the horizontal axis. This tail replaced the exponential tail given by (11). Using this straight-line adjustment to the Kaplan-Meier estimator, the PC procedure yielded a correlation of $r = .109$ with an estimated one-sided significance probability of $P = .112$ (based on 1000 permutations). The corresponding values, using the exponential tail for the Kaplan-Meier estimator, were $r = .198$ and $P = .017$. The overall indication, from the PC procedures, is that of a modest, but significant, positive correlation between transplant date and post-transplant survival.

We obtained another measure of trend in post-transplant survival as follows. Table 6, in the form of a 2×4 contingency table,

gives, for each of the years 1968, 1969, 1970, 1971, the number of patients (M) who were accepted as candidates in that year and went on to receive a transplant. It also provides the number (m) of those who survived at least one year after their transplant. (We omitted 1972 to simplify the analysis; complete returns on the 1972 group were not available at the March 1, 1973 closing date.)

Table 6. Relationship between year of acceptance and one-year post-transplant survival rate.

year i	1(1968)	2(1969)	3(1970)	4(1971)
m_i	2	6	2	6
M_i-m_i	7	5	4	7
M_i	9	11	6	13

Employing a procedure due to Armitage [1], we used Kendall's S to test for a trend in the one-year survival rates. The statistic S reduces to

$$S = (M_1-m_1)(m_2+m_3+m_4) + (M_2-m_2)(m_3+m_4) + (M_3-m_3)m_4$$
$$- m_1\{(M_2-m_2) + (M_3-m_3) + (M_4-m_4)\} - m_2\{(M_3-m_3)$$
$$+ (M_4-m_4)\} - m_3(M_4-m_4) .$$

Under the hypothesis of no trend, the mean of S is zero and variance of S is

$$Var(S) = \frac{t(T-t)}{3T(T-1)} (T^3 - \Sigma M_i^3) ,$$

where $t = \Sigma m_i$ and $T = \Sigma M_i$. For the data of Table 6, $S = 50$, $Var(S) = 4539.6$, and the normal deviate is .74 corresponding to a one-sided P value of .23. This analysis, based on much less information than PC procedures, agrees in direction--but not in degree of significance--with the PC results that suggested a positive trend in post-transplant survival.

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REFERENCES

[1] P. ARMITAGE, Tests for linear trends in proportions and frequencies, Biometrics, 11(1955), pp. 375-386.

[2] I. A. CLARK, F. B. STINSON, R. B. GRIEPP, J. S. SCROEDER, E. E. SHUMWAY, D. C. HARRISON, Cardiac transplantation in man. VI. Prognosis of patients selected for cardiac transplantation, Ann. Intern. Med., 75(1971), pp. 15-21.

[3] D. R. COX, Regression models and life-tables, J. R. Statist. Soc. B, 34(1972), pp. 187-220.

[4] H. E. DANIELS, The relation between measures of correlation in the universe of sample permutations, Biometrika, 33(1944), pp. 129-135.

[5] E. DONG, Personal Communication, (1973).

[6] B. EFRON, The two sample problem with censored data, Proc. 5th Berkeley Symp., 4(1967), pp. 831-853.

[7] M. E. GAIL, Does cardiac transplantation prolong life? A reassessment, Ann. Intern. Med., 76(1972), pp. 815-817.

[8] N. A. GEHAN, A generalized Wilcoxon test for comparing arbitrarily single-censored samples, Biometrika, 52(1965), pp. 203-224.

[9] M. HOLLANDER and D. A. WOLFE, Nonparametric Statistical Methods, Wiley, New York, 1973.

[10] L. KAARSEMAKER and A. VAN WIJNGAARDEN, Tables for use in rank correlation, Statist. Neerl., 7(1953), pp. 41-54.

[11] E. L. KAPLAN and P. MEIER, Nonparametric estimation from incomplete observations, J. Amer. Statist. Ass., 53(1958), pp. 457-481

[12] M. G. KENDALL, Rank Correlation Methods, Fourth Edition, Griffin, London, 1970.

[13] B. J. MESSMER, J. J. NORA, R. D. LEACHMAN, and D. A. COOLEY, Survival-times after cardiac allografts, Lancet, May (1969), pp. 954-956.

[14] B. W. TURNBULL and B. W. BROWN, JR., Survivorship analysis of heart transplant data, Stanford University Department of Statistics Technical Report No. 34, (197[illegible].

[15] B. W. TURNBULL, B. W. BROWN, JR., and M. HU, Survivorship analysis of heart transplant data (Revision of [14]), (1973).